REMARKS

Applicant made various amendments to claims 1 and 8 and submitted new claims in the response to the Office Action submitted September 12, 2004. In response to this response, an Office Communication was issued indicating Applicant did not identify whether the amendments represent new matter and if they do not, portions of the specification must be identified as supporting the new claim language. Applicant's respectfully disagree as indicated below.

In the response filed on September 12, 2004, Applicant indicated on page 8, lines 5-6, that "The Applicant submits that the amendment does not constitute new matter." As such, Applicant stated that no new matter had been added. Furthermore, Applicant points to paragraphs 0020 and 0024 in the specification as support for the amendments to claims 1 and 8. Additionally at the bottom of page 11 of the response, Applicant states "Claims 9 and 17 are supported by paragraph 0066. Claim 10 is supported, by section in (a) in Example 3, (b) paragraphs 0033 amd 0038, (c) paragraph 00339, (d-e) the computer appendix, (f) paragraph 0039, (g) paragraphs 0042-3 and (h) the computer appendix. Claims 11-15 parallel claims 2-6. Claim 16 is supported by the computer program. Claim 18 is supported by paragraph 0027."

Another copy of the Office Action submitted is enclosed for reference. In view of the above identified portions of the response, no new matter has been added and support for the new claims has been identified in the specification, thus it is believed that all issued raised in the Office Communication have been dealt with. If this response does not address the Office Communication's issues, it is kindly requested that a new Office Communication be issued that provides more specificity so that the Applicant can respond directly to the issues.

If the Examiner believes that a telephone conference with Applicant's representative might expedite prosecution of the application, he is cordially invited to call at the number listed below.

Dated: 10/15/04

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Docket No.: BUCSD - 1025958

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of	)	FOR: METHODS FOR PREDICTING PROTEIN-PROTEIN INTERACTIONS IN ENTIRE PROTEOMES
David A. GOUGH and Joel R. BOCK	)	
Serial No.: 09/993,272	)	
Filed: November 14, 2001	)	Group Art Unit: 1631

AMENDMENT

Commissioner for Patents
P. O. Box 2327
Arlington VA 22202

Attention: Michael L Borin, PhD
Examiner

Dear Examiner Borin:

This is in response to the Office Action dated January 15, 2004. Please amend the above-identified application as follows:

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Arlington VA 22202 on

~~September 8, 2004~~ July 8 04
(Mailing Date)

Cindy Guido
(Typed Name)

(Signature)

September 8, 2004
(Date of Signature)

IN THE TITLE

Please amend the title to read as follows:

(amended) METHOD FOR PREDICTING MACROMOLECULAR INTERACTIONS BASED ON PRIMARY SEQUENCE DATA ~~PREDICTING PROTEIN-PROTEIN INTERACTIONS IN ENTIRE PROTEOMES~~

IN THE SPECIFICATION

[0017] FIGURE 1. Scatterplot showing detail view of sample data points $x_i \in R^n$ representing *H. pylori* ~~protein~~ protein-protein interactions, visualized by two dimensional Sammon mapping. Circled points indicate incorrect decisions made during leave-one-out prediction error estimation. 90% of all data points (1,873/2,077) ~~appearl~~ appear in this map. Coordinate axes contain arbitrary units. Estimated system generalization error rate is 12.04%.

IN THE CLAIMS

1. (amended) A method for predicting biomolecular interactions comprising,

inputting a first set of biomolecules into a trainable system, wherein the first set comprises primary structures of a training set ~~primary structure~~ of biomolecules with known interactions, and the trainable system comprises a support vector learning machine ~~comprising into a trainable system~~,

teaching the trainable system using known interaction domains between members of the first set of biomolecules and assign a value for binding of the interaction domains to each other, wherein the binding of the domains is indicated by a minimum threshold value,

inputting a second set of biomolecules into the trainable system, wherein the second set comprises primary structures of a set of biomolecules with unknown interactions ~~into the trainable system~~, and

predicting interactions between members of the second set of biomolecules ~~with unknown interactions~~ by analyzing at least one fragment of a first biomolecule of the second set and assigning a value for binding to at least one fragment of a second biomolecule of the second set and assigning a value for binding of the first fragment to the second fragment wherein binding is indicated by a value at least equal to the minimum threshold value ~~by analogy to the biomolecules in the training set using the trainable system~~.

2. (original) The method of claim 1, wherein the interactions are homotypic.

3. (original) The method of claim 1, wherein the interactions are heterotypic.

4. (original) The method of claim 1, wherein the biomolecule is a protein.

5. (original) The method of claim 1, wherein the biomolecule is a nucleic acid.

6. (original) The method of claim 1, wherein the biomolecule is a bioactive agent.

7. (cancelled)

8. (amended) A trainable system for predicting biomolecular interactions comprising,

a training set comprising primary structure of a first set of biomolecules with known interactions ~~into a trainable system~~,

an algorithm for quantifying interactions between biomolecules known to interact,

a set of biomolecules with unknown interactions wherein the biomolecules are represented as a linear set of features ~~into the trainable system~~, ~~and~~

a system for predicting interactions between members of the set of biomolecules with unknown interactions wherein the system performs a series of pairwise comparisons between each biomolecule of the training set with each biomolecule of the unknown interaction set and predicts interaction between the biomolecules of the unknown interaction set by analogy to the biomolecules in the training set ;and

the trainable system comprises a support vector learning machine.

9. (new) The method of claim 1, wherein the training set further comprises pairs of biomolecules known to not interact.

10. (new) A method for predicting biomolecular interactions comprising:

a) inputting a set of biomolecules with known interactions into a trainable system, wherein each biomolecules comprises a series of features ;

b) representing the biomolecules by data vectors of features wherein the features comprise primary structure of the biomolecules and associated

physicochemical properties of each element of the primary structure in sequence;

c) assembling paired sets of features to allow comparison of the features to each other;

d) training the trainable system using a deterministic optimization algorithm by introducing pairs of known interactions and labels indicating a positive interaction status to develop a pattern recognition system;

e) optimizing the pattern recognition system by performing a systematic computational search over a range of model parameters;

f) inputting features of biomolecules with unknown interactions into the trained system;

g) predicting labels of biomolecules with unknown interaction status by using the trained system;

h) estimating statistical confidence in the predictions using cross validation errors obtained in the optimization process.

11. (new) The method of Claim 1, wherein the interactions are homotypic.

12. (new) The method of Claim 1, wherein the interactions are heterotypic.

13. (new) The method of Claim 1, wherein at least one biomolecule is a protein.

14. (new) The method of Claim 1, wherein at least one biomolecule is a nucleic acid.

15. (new) The method of Claim 1, wherein at least one biomolecule is a bioactive agent.

16. (new) The method of Claim 1, wherein the trainable system is a support vector machine (SVM) comprising:

a) a collection of support vectors identified during an optimization process to define boundaries of a statistical decision surface used to discriminate input features;

b) a linear combination of these support vectors;

c) parameters defining the location and orientation of the decision surface in high-dimensional feature space; and

d) an analytical upper bound on the generalization error associated with a set of novel features input to the trained SVM.

17. (new) The method of Claim 1, wherein the training set further comprises pairs of biomolecules known to not interact.

18. (new) The method of Claim 1, wherein the set of biomolecules is from a complete genome.

REMARKS

The Applicants thank the Examiner for his careful analysis of the specification and claims. The Applicants have amended the claims as shown above and submit that the application is now in a proper form for allowance.

The Applicants have amended the title to more clearly reflect the subject matter claimed after restriction of the claims. The Applicants submit that the amendment does not constitute new matter.

The Applicants have amended paragraph 0017 to correct typographical errors that are obvious. The Applicants submit that the amendment does not constitute new matter.

The Examiner has rejected claims 1-6 and 8 under 35 U.S.C. 112, paragraph 2 for being indefinite and failing to particularly point out and distinctly claim the matter that the Applicants regard as the invention. Claims 1and 8 have been substantially amended to increase clarity and comply with the requirements of 35 U.S.C. 112, paragraph 2. Therefore the rejection is traversed.

A trainable system is defined in paragraph 0020 of the instant application. It is a system that "can "learn" to determine patterns and that will allow for prediction of outcomes, upon analysis of unknowns similar to those in the training set." In the instant invention, "a training set" teaches "the trainable system about biomolecular interactions by providing examples of how proteins interact with each other by providing a number of examples of protein-protein interactions." (paragraph 0024). This process is described in more detail in Example 2 and supported in the computer appendix which is incorporated into the specification by reference.

The Examiner has rejected claims 1-8 for both anticipation and obviousness under 35 USC § 102 and § 103, respectively in view of Brauheim. The Examiner has further rejected all of the claims for obviousness in view of the admitted prior art. The Applicants submit that the instant invention is clearly distinct from the teachings of both Braheim and the admitted prior art, which will be addressed independently.

The Applicants submit that there are at least three substantial differences between the instant invention as now claimed and the teachings of the Brauheim patent.

1. The Brauheim patent is neural network specific;
2. The Brauheim patent requires a 3-dimensional surface or geometric data inputs; and
3. The Brauheim patent predicts binding energy exclusively.

The claims to the instant invention are directed to the use of support vector machines, taught in the specification to be superior to other trainable systems in Example 2; using primary sequence information; to predict biomolecular binding without requiring a prediction of binding energy. Therefore, the instant invention is clearly distinguished from the teachings of the Brauheim reference.

The use of primary structure information, rather than tertiary structural information, is a substantial advantage of the invention over the prior art. The use of primary structures is discussed in the first paragraph of the summary of the invention, paragraph 0013. The advantages of using primary sequence data are discussed in paragraph 0014. Primary structure is defined in paragraph 0023. One of the main advantages is that primary structure information (e.g. amino acid sequence) is available for far more proteins than structural information. This advantage becomes increasingly important because of the amount of primary sequence data being derived from the various genome programs. Moreover, the use of primary sequence data also allows for the prediction of interactions of membrane proteins which are notoriously difficult to analyze structurally. Therefore, the method of the instant invention can be used for the prediction of interactions between far more proteins.

The Brauheim method uses neural networks that are "trained to recognize the quantum mechanical electrostatic potential and geometry at the entire van der Waals surface of a group of training molecules and to predict the strength of interactions, or free energy of binding." (col 2, ln 19-22). Brauheim states that in his method "The entire

surface of each molecule, represented by a discrete collection of points, serves as the input to the neural network. In this way the invention utilizes quantum mechanical means to describe the molecular activity of a compound of interest." Therefore, Brauheim sees the use of the 3-dimensional surface as an advantage of his invention. Therefore, it would not be obvious to modify the method of Brauheim to use primary sequence data to predict interactions.

The instant invention predicts interactions based on meeting a specific threshold rather than by predicting a binding energy. Therefore the determination of an interaction is binary, either meeting the threshold or not, as opposed to determining a binding energy for the pairing. One would not be motivated to modify Brauheim to produce such a binary result.

In view of these substantial differences between the claims of the instant invention and the teachings of Brauheim, the Applicants submit that claims 1-6 and 8 are clearly distinguished from the teachings of Brauheim; therefore, the rejections for anticipation and obviousness under 35 USC § § 102 and 103 are traversed.

The Examiner has stated that the claims of the instant invention are obvious in view of the admitted prior art. The Examiner has made no specific comments regarding the application of the references to the claims. Therefore, the response made to the rejection concerns broad concepts, rather than specific, detailed responses. The Applicants request that if the Examiner deems the response insufficient that he make more specific rejections in the future to allow the Applicants to make a more appropriate response.

The Applicants submit that none of the references cited in the specification suggest or make obvious the method of the invention for the reasons detailed below.

Champion (2001), Fields and Song (1989) and McBeath and Schreiber (2000) all require the use of proteins and determination of interactions by contacting proteins with each other. This is clearly distinct from the computational method of the instant invention.

Enright (1999) requires that gene fusion events can be identified using a fusion

detection algorithm as a step to predict protein-protein interactions. This requires the use of whole genomes, which is either not possible, or at least impractical for most higher organisms.

Joachims (1999), Schoelkopf (1999) and Vapnik (1995) teach support vector machines for any use and do not include any teachings regarding protein-protein interactions.

Sankoff (1992), and Tekaia (1999) are concerned with evolution rather than protein-protein interactions, and require substantial amounts of genomic sequence information from multiple organisms to perform their analysis. This is distinct from the instant invention that can use any of a number of possible training sets.

Woese (1990) proposes a new phylogenetic tree, but does not propose a method for analysis of macromolecular interactions.

The Applicants submit that the claims of the instant invention are not obvious in view of the admitted prior art, either alone or in combination with each other, for the above reasons. Therefore, the rejection for obviousness under 35 USC § 103 is traversed.

The Applicants have added a number of claims. Support for all of the claims can be found in the specification and in the computer appendix that is incorporated by reference into the specification.

Claims 9 and 17 are supported by paragraph 0066. Claim 10 is supported, by section in (a) in Example 3, (b) paragraphs 0033 and 0038, (c) paragraph 0039, (d-e) the computer appendix, (f) paragraph 0039, (g) paragraphs 0042-3 and (h) the computer appendix. Claims 11-15 parallel claims 2-6. Claim 16 is supported by the computer program. Claims 18 is supported by paragraph 0027. The Applicants submit that these claims are both novel and non-obvious in view of the prior art.

FEES

The Applicants have authorized the Commissioner to charge the Deposit Account

indicated the amount of $475 to cover the fees for a request for a three month extension. It is believed that no additional fee is due. However, if a fee is due, the Commissioner is hereby authorized to charge Deposit Account 50-1990, referencing case number BUCSD 1025958.

CONCLUSIONS

In view of the forgoing amendments and arguments, the Applicants submit that the application is now in proper form for allowance. However, if there are any outstanding issues remaining in the case that can be resolved by telephone, the Examiner is encouraged to call the Agent for Applicant below, collect, to discuss the outstanding issues.

Respectfully submitted,

Dated: July 8, 2004

By: _____
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Docket No.: BUCSD 1025958